



A New Insight into the Role of CART in Cocaine Reward: Involvement of CaMKII and Inhibitory G-Protein Coupled Receptor Signaling

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Cocaine- and amphetamine-regulated transcript (CART) peptides are neuropeptides that are expressed in brain regions associated with reward, such as the nucleus accumbens (NAc), and play a role in cocaine reward. Injection of CART into the NAc can inhibit the behavioral effects of cocaine, and injecting CART into the ventral tegmental area (VTA) reduces cocaine-seeking behavior. However, the exact mechanism of these effects is not clear. Recent research has demonstrated that Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) and inhibitory G-protein coupled receptor (GPCR) signaling are involved in the mechanism of the effect of CART on cocaine reward. Hence, we review the role of CaMKII and inhibitory GPCR signaling in the effect of CART on cocaine reward and provide a new insight into the mechanism of that effect. In this article, we will first review the biological function of CART and discuss the role of CART in cocaine reward. Then, we will focus on the role of CaMKII and inhibitory GPCR signaling in cocaine reward. Furthermore, we will discuss how CaMKII and inhibitory GPCR signaling are involved in the mechanistic action of CART in cocaine reward. Finally, we will provide our opinions regarding the future directions of research on the role of CaMKII and inhibitory GPCR signaling in the effect of CART on cocaine reward.

Keywords: CART, cocaine addiction, CaMKII, GABA_BR, D₃R

INTRODUCTION

Cocaine is a strong psychostimulant drug that can inhibit the reuptake of serotonin, norepinephrine and dopamine (DA). This results in greater concentrations of these three neurotransmitters in the brain. The drug can easily cross the blood-brain barrier and cause the user to feel intense euphoria (Pomara et al., 2012). In 2014, 18.3 million people were using cocaine worldwide. Cocaine can be administered by smoking, intravenous injection or inhalation, all of which can produce intense euphoric effects (United Nations Office on Drug and Crime (UNODC), 2016). Unfortunately, this euphoria can lead to increased frequency of use and dosage to obtain the same effect and to avoid the uncomfortable physiological and psychological effects linked to the cessation of drug use

TABLE 1 | The evidence that cocaine- and amphetamine-regulated transcript (CART) plays an important role in cocaine reward.

Species	Methods	Results	Mechanisms	References
Rat	Cocaine administration	CART expression ↑ in brain regions associated with reward	cAMP/PKA/CREB	Lakatos et al. (2002) and Cho et al. (2017)
Rat	Intra-NAc CART	Locomotor activity ↓	Inhibits the influx of Ca ²⁺	Jaworski et al. (2003) and Peng et al. (2014)
Rat	Intra-NAc CART	Self-administration ↓	Ca ²⁺ /CaMKII, D3R	Jaworski et al. (2003) and Jaworski et al. (2008)
Rat	Intra-paraventricular thalamus CART	Cocaine-seeking behavior ↓	Unclear	James et al. (2010)
Monkey	Cocaine administration	CART expression ↑ in brain regions associated with reward	cAMP/PKA/CREB	Nader et al. (2002)
Human	Genetic studies	Contributed to the etiology of cocaine dependence	Unclear	Lohoff et al. (2008)

(Hou et al., 2014). Long-term and repeated cocaine use harms human health and contributes to crime, which places a great burden on families and society. However, the problem of cocaine abuse continues to spread. Therefore, there is an urgent need for new treatments to control and reduce the harm of cocaine abuse.

Cocaine- and amphetamine-regulated transcript (CART) is a neuropeptide that is expressed in brain regions associated with reward, such as the nucleus accumbens (NAc). During the last two decades, increasing evidence has demonstrated that CART plays a role in cocaine reward (Table 1). First, high densities of CART-containing nerve terminals are localized in brain regions associated with reward (Fagergren and Hurd, 2007). Second, injection of CART into the NAc can attenuate the behavioral effects of DA and cocaine (Hubert et al., 2008). Third, injection of CART into the paraventricular thalamus (PVT) can suppress cocaine-seeking behavior in rats (James et al., 2010). However, the mechanism by which CART inhibits the behavioral effect of DA is still not clear. Recently, some research has shown that Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) and inhibitory G-protein coupled receptor (GPCR) signaling are involved in the mechanism of the effect of CART on cocaine reward, which may explain how CART inhibits the behavioral effect of DA and may help establish a more comprehensive mechanistic model of the effect of CART on cocaine reward. In the following sections, we will first review the role of CART in cocaine reward and note the shortcomings of the currently proposed mechanism for the effect of CART on cocaine reward. Then, we will focus on the role of CaMKII and inhibitory GPCR signaling in cocaine reward. In addition, we will discuss how CaMKII and inhibitory GPCR signaling are involved in the mechanism of the effect of CART on cocaine reward. Finally, we will provide our opinions regarding the future directions of research on the role of CaMKII and inhibitory GPCR signaling in the effect of CART on cocaine reward.

ROLES OF CART IN COCAINE REWARD

The Biological Features of CART

Douglass et al. (1995) used differential display PCR to screen for specific mRNAs that are transcriptionally regulated by cocaine and amphetamine in specific brain regions in rats. The authors

identified a previously uncharacterized mRNA that was extracted from the hypothalamus by Spiess et al. (1981) and named it CART (Zhang et al., 2012). In addition to the brain, CART is also expressed in the pituitary gland, adrenal medulla and pancreas in humans. The CART peptide contains 116 amino acids encoded by the *cart* gene, which is located on the 5th chromosome in humans (Robson et al., 2002). The *cart* gene is approximately 2 kbp in length and contains two introns and three exons. There is a cyclic adenosine monophosphate (cAMP) response element (CRE) in the start codon of the *cart* gene (Perry Barrett et al., 2002). Therefore, CART could be upregulated by cocaine through the cAMP/protein kinase A (PKA)/CRE binding protein (CREB) signaling pathway. In addition to humans, the CART peptide has been found in other species, such as goldfish and mouse (Volkoff and Peter, 2001; Zhang et al., 2012). However, compared with humans, there are two alternatively spliced variants within exon 2 of rCART. In goldfish, there are also two CART peptides. These two CART peptides originate not from alternative splicing but from the expression of two CART genes (Volkoff and Peter, 2001). Meanwhile, the sequence of the rat CART gene shows great homology with the human gene (Zhang et al., 2012). Many studies have demonstrated that the CART peptide can attenuate the behavioral effects of DA and cocaine and plays an important role in reward and reinforcement. In addition, the CART peptide is involved in feeding, stress and the regulation of the endocrine system (Asakawa et al., 2001; Kong et al., 2003; Larsen et al., 2003; Kuriyama et al., 2004; Koylu et al., 2006).

CART Abnormalities in Cocaine Administration

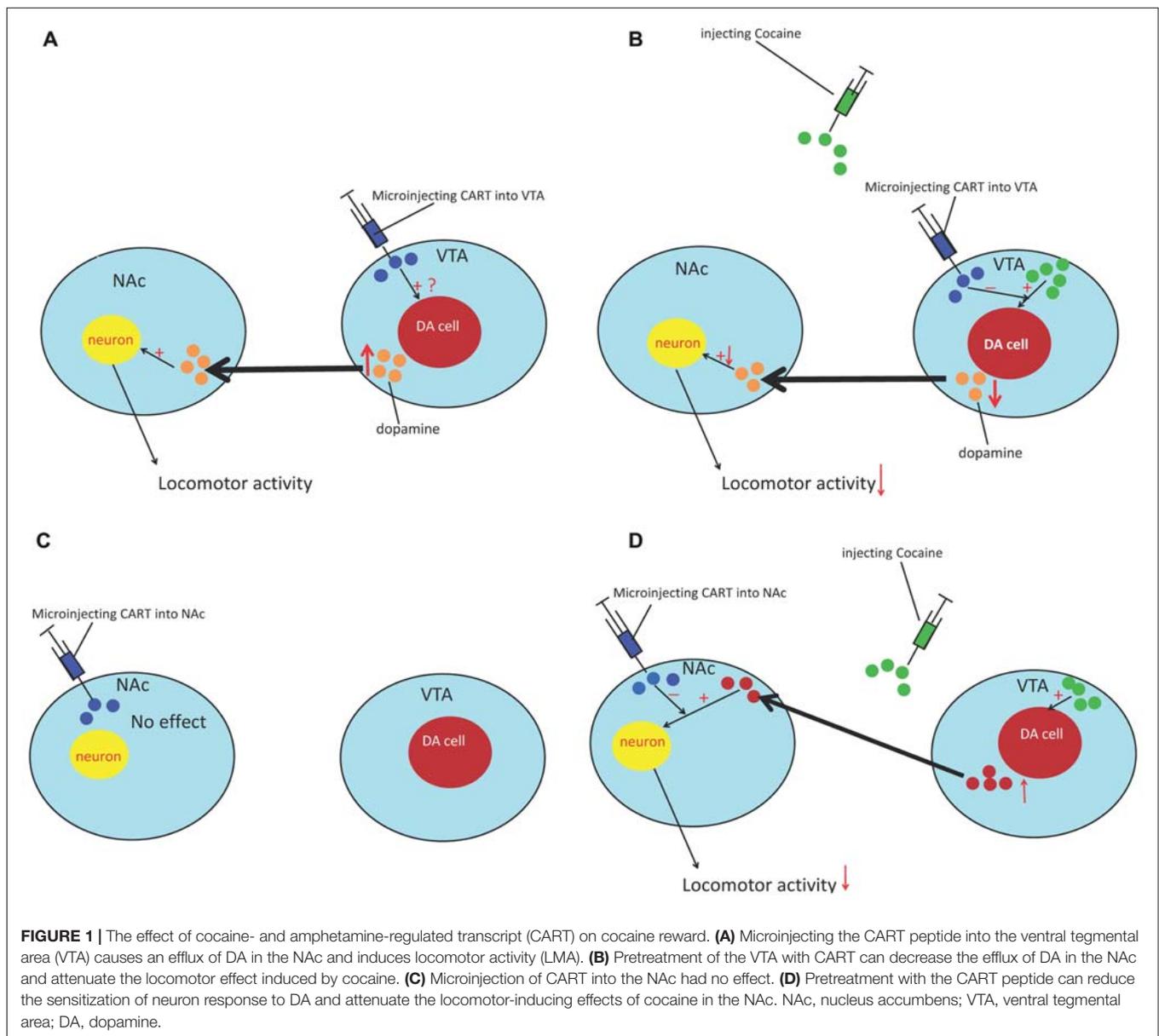
CART mRNA has been found to be upregulated by cocaine or amphetamine in the rat striatum (Volkoff and Peter, 2001). However, this result has not been consistently replicated (Vrang et al., 2002). Hunter et al. (2005) have demonstrated that chronic and acute administration of cocaine failed to upregulate the levels of CART mRNA or peptide, but binge administration of cocaine resulted in increased CART mRNA in the NAc. The involvement of corticosterone may account for the abovementioned inconsistent results (Hunter et al., 2005). Binge administration of cocaine could cause significant stress to

the rats, and corticosteroids are involved in stress. Meanwhile, Hunter et al. (2005) found that corticosterone administration produced a significant increase in CART mRNA, which suggests that CART mRNA may be regulated by cocaine under certain conditions, such as binge administration, and this may at least partly involve corticosterone. As estradiol may interact with the DA system, there is also a sex difference in the effect of cocaine on CART. Fagergren and Hurd (1999) found that CART levels were elevated in the medial accumbens shell and the central amygdala of male but not female rats after the administration of cocaine (Rodrigues et al., 2011). Additionally, this research showed that CART mRNA expression did not exhibit marked alterations in specific regions of the rat brain during the early phase of cocaine self-administration (Rodrigues et al., 2011). Furthermore, CART expression levels were increased in the NAc

of human cocaine abusers (Albertson et al., 2004; Bannon et al., 2005).

The Effect of CART on Cocaine Reward

Injection of CART peptide into the accumbens had no effect on locomotion (Kuhar et al., 2005). However, intra-accumbal CART attenuated the locomotor activity (LMA) produced by systemic cocaine and amphetamine administration. As cocaine induces LMA by potentiating dopaminergic transmission, the effect of CART 55-102 on DA-induced LMA was examined to explain the abovementioned phenomenon. As expected, CART peptide dose-dependently attenuated locomotion produced by intra-accumbal infusions of DA. These studies suggested that CART attenuates cocaine-induced LMA by attenuating the behavioral effect of DA. Meanwhile, intra-ventral tegmental



area (VTA) injection of CART induced LMA and promoted conditioned place preference. The effect on LMA was dose dependent and was blunted by a DA receptor antagonist (Kimmel et al., 2000). However, pretreatment of the VTA with CART attenuated the locomotor effect induced by cocaine administration (Jaworski et al., 2007). Regarding the different results in the NAc and VTA, the potential mechanism may involve the cell bodies of the mesolimbic system that are located in the VTA; CART can produce weak psychostimulant-like effects and causes an efflux of DA in the NAc, which produces weak LMA (Kuhar et al., 2005) and suggests that CART can activate the DA system, but not in the same manner as cocaine (Figure 1). Meanwhile, this inhibitory effect of CART peptide also generalizes to other measures of dopaminergic function such as reward/reinforcement. Jaworski et al. (2008) found that injecting CART into the NAc could reduce cocaine self-administration in rats. Furthermore, James et al. (2010) reported that injection of CART into the PVT could suppress cocaine-seeking behavior in rats (James et al., 2010). However, the mechanisms through which CART influences the DA system are still unclear. Therefore, in the following sections, we provide a putative mechanism that involves CaMKII and inhibitory GPCR signaling to explain this abovementioned phenomenon.

ROLES OF CaMKII IN COCAINE REWARD

The Biological Features of CaMKII

CaMKII is a holoenzyme composed of subunits expressed by four genes (α , β , γ and δ ; Rosenberg et al., 2010). This enzyme is abundant in brain cells, especially at the synapse. In the rat forebrain, there are two isoforms of CaMKII α and CaMKII β . The functions and expression features of CaMKII α and CaMKII β are different; CaMKII α is expressed specifically in glutamatergic neurons (Liu and Murray, 2012), and the activity of α CaMKII is vital for memory formation and synaptic plasticity (Yamagata et al., 2009). CaMKII β is distributed in inhibitory interneurons and glutamatergic neurons (Lamsa et al., 2007). Activated CaMKII can phosphorylate its own autophosphorylation site (T286 in the isoform). Thus, CaMKII can convey information by diverse forms of Ca²⁺ transients and serve as a dynamic regulator that converts activity-dependent Ca²⁺ signals into different forms of plasticity and synaptic activity (Hudmon and Schulman, 2002; Colbran and Brown, 2004; Griffith, 2004). Recently, many studies have demonstrated that Ca²⁺ and Ca²⁺-regulated second messenger systems are involved in the behavioral response to cocaine in animals, and CaMKII plays an important role in the behavioral response to cocaine (Licata et al., 2004; Miller and Marshall, 2004).

CaMKII and Cocaine Behavioral Sensitization

Cocaine can block the reuptake of DA and result in the accumulation of DA in the synaptic cleft. The accumulated DA can then promote glutamate release, which activates NMDA

receptors and causes Ca²⁺ influx through NMDA receptors as well as L-type Ca²⁺ channels by activating D₁ receptors and desensitizing D₃ receptors (Wakabayashi and Kiyatkin, 2012). The influx of Ca²⁺ causes the activation of CaMKII, which promotes the phosphorylation of various targets and produces different biological effects, such as promoting the influx of Ca²⁺ and producing locomotion (Easton et al., 2014). Previous studies have shown that injecting an L-type Ca²⁺ channel antagonist can inhibit the expression of a sensitized behavioral response to amphetamine or cocaine (Park et al., 2001; Mills et al., 2007). Meanwhile, a great deal of research has shown that the overexpression of α CaMKII promotes behavioral sensitization to cocaine. Furthermore, injection of a CaMKII inhibitor (KN-93) into the VTA blunts the behavior sensitization produced by cocaine; consistent with KN-93 findings, behavioral sensitization to cocaine was attenuated in α CaMKII knockdown mice (Licata et al., 2004; Zhen et al., 2007; Kadivar et al., 2014). Together, these data demonstrate that CaMKII activity induced by the influx of Ca²⁺ can regulate behavioral sensitization to cocaine.

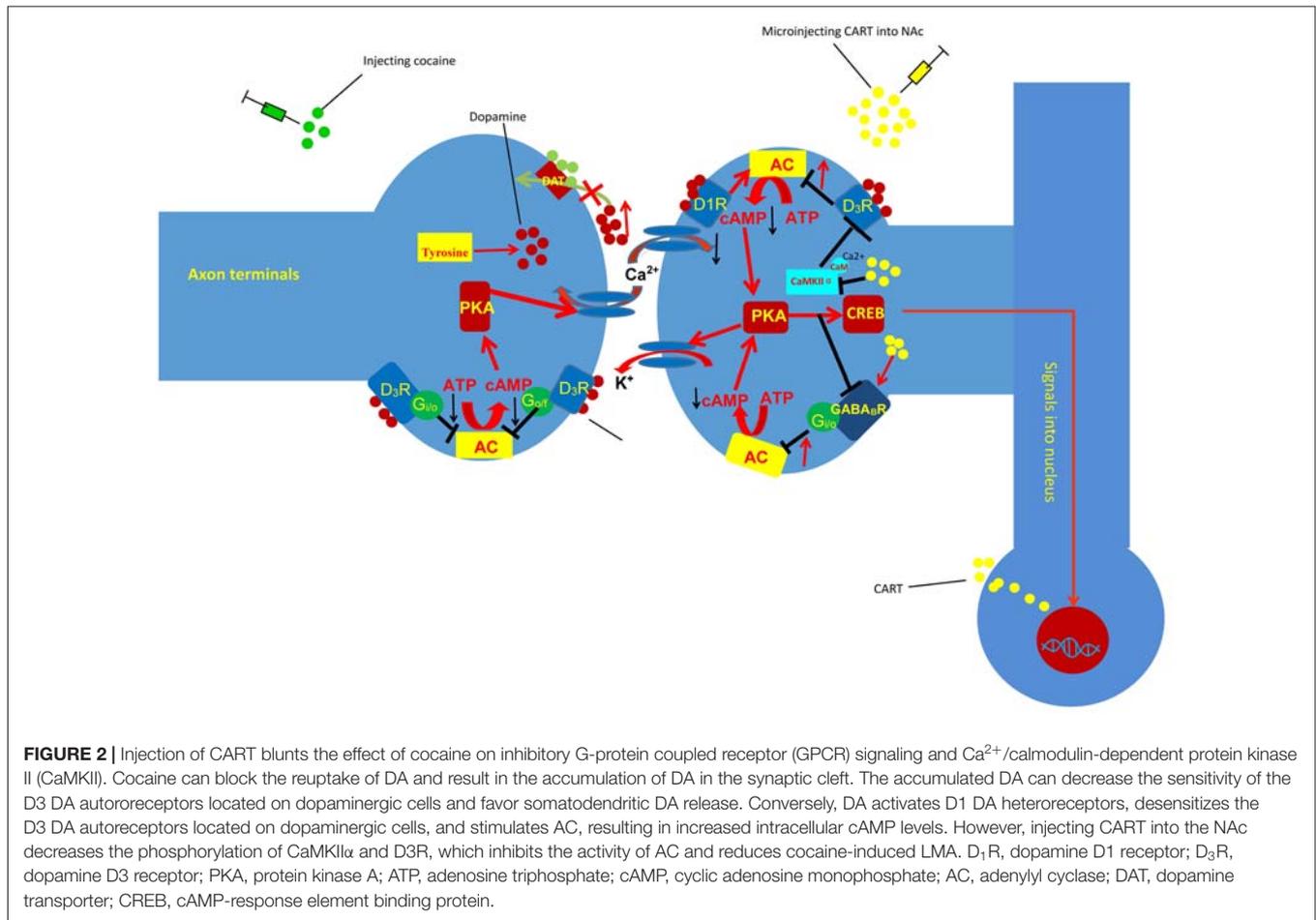
CaMKII and Cocaine-Associated Memories

Individuals frequently encounter environmental cues previously associated with drug use that can increase craving and the likelihood of relapse (Fuchs et al., 2009; Kalivas, 2009). The ability of drug-associated memories to induce relapse is perhaps the greatest obstacle to the successful treatment of addictive disorders. Previous work has revealed that a single cocaine exposure can induce neuronal activation and long-term potentiation (LTP) in the VTA (the phosphorylation of CaMKII is very important for the induction of LTP; Ungless et al., 2001). Meanwhile, cocaine administration can increase the phosphorylation of CaMKII, and intra-VTA inhibition of CaMKII before cocaine conditioning blocks the acquisition of cocaine conditioned place preference (Liu et al., 2014; Schöpf et al., 2015). Together, those results suggest that CaMKII plays an important role in the formation of cocaine-associated memories. Furthermore, Rich et al. (2016) found that intra-basolateral amygdala inhibition of CaMKII promoted the extinction of cocaine-associated memory and led to a reduction in subsequent cue-induced reinstatement, which provides a novel target for preventing relapse to cocaine use.

ROLES OF INHIBITORY G-PROTEIN COUPLED RECEPTOR SIGNALING IN COCAINE REWARD

The Biological Features of Inhibitory G-Protein Coupled Receptor Signaling

GPCRs are seven-transmembrane-domain receptors, which transduce ligand-binding events into intracellular responses. Depending on the α subunit type, GPCRs can be *Gas*, *Gai/o*, *G α q/11* or *G α 12/13* (Wettschureck and Offermanns, 2005; Oldham and Hamm, 2008). *Gai/o* can interact with downstream effectors and inhibit excitatory effectors, including most isoforms of adenylyl cyclase (AC) and some types of voltage-gated



Ca²⁺ channels. Metabotropic γ -aminobutyric acid receptors (GABA_BRs) and D₃ receptors couple to and activate the Gi/o subclass of G α subunits and produce inhibitory signaling (Filip et al., 2007). Currently, increasing evidence has indicated that inhibitory GPCR signaling mediated by the Gi/o class of GPCRs for the neurotransmitters GABA (GABA_BR) and DA (D₃ receptors) plays an important role in cocaine reward (Goldstein and Volkow, 2002; Vlachou and Markou, 2010; **Figure 2**). Many studies have shown that GABA_BR, D₃R and CART are co-expressed in some brain regions, such as the NAc (Liu et al., 2009; Hubert et al., 2010; Fu et al., 2016). Meanwhile, some research has demonstrated that GABA_BR and D₃Rs can interact with CART (Hubert et al., 2010; Peng et al., 2014; Fu et al., 2016). Therefore, GABA_BRs and D₃Rs, as representative inhibitory GPCR signaling are chosen to illustrate the involvement of inhibitory GPCR signaling in the role of CART in cocaine reward.

GABA_BR and Cocaine Reward

GABA_BRs are metabotropic receptors that belong to the GPCR superfamily and are responsible for the neuromodulation of GABA (Yamaguchi et al., 2002). The GABA_BRs are distributed at pre- and post-synaptic sites. The activation of presynaptic GABA_BRs can block calcium channels. The activation of

post-synaptic GABA_BRs activates potassium channels and increases the flux of potassium from extracellular to intracellular sites. Chronic cocaine administration decreases the functional coupling of GABA_B receptors in the rat brain (Kushner and Unterwald, 2001; Jayaram and Steketee, 2004). Meanwhile, the GABA_BR agonist baclofen attenuates cocaine-induced hyperlocomotion, and intra-VTA application of baclofen blunts cocaine self-administration (Brebner et al., 2000). Furthermore, clinical research has shown that baclofen can attenuate cue-associated cocaine craving and reduce cocaine use in a double-blind placebo-controlled trial (Shoptaw et al., 2003).

D₃R and Cocaine Reward

D₃Rs are GPCRs and belong to the class of D₂-like receptors, which can inhibit AC and negatively modulate the activity of PKA and its effectors (Rangel-Barajas et al., 2015). In humans, D₃Rs are expressed in the islands of Calleja, ventral striatum/NAc, dentate gyrus and striate cortex (Heidbreder et al., 2005). Compared with D₂ receptors, D₃Rs have a high affinity for DA. Small changes in their number or function may lead to dramatic effects on synaptic transmission, suggesting that D₃ receptors could be critical for modulating dopaminergic function. Many studies found that a D₃R agonist (BP897) blunted cocaine-seeking behavior during the presentation of

cocaine-associated cues in rats (Cervo et al., 2003; Gilbert et al., 2005; Cortés et al., 2016). Furthermore, increasing evidence has shown that selective D₃ receptor agonists can attenuate cocaine self-administration (Beardsley et al., 2001; Cheung et al., 2013). Altogether, these studies indicate that D₃Rs play a vital role in cocaine addiction and may be a potential target for drug treatments.

THE INTERACTION OF CART WITH CaMKII AND D₃R AFTER REPEATED COCAINE ADMINISTRATION

Repeated cocaine administration decreases the sensitivity of the D₃ DA autoreceptors located on dopaminergic cells and reduces G-protein-mediated K⁺ efflux, which favors somatodendritic DA release (Licata and Pierce, 2003). Conversely, DA activates D₁ DA heteroreceptors, desensitizes the D₃ DA autoreceptors located on dopaminergic cells, and stimulates AC, resulting in increased intracellular cAMP levels (Licata and Pierce, 2003). The increased intracellular cAMP levels can then activate PKA and ultimately upregulate the expression of CART via the cAMP/PKA/CREB signaling pathway (Lakatos et al., 2002). Meanwhile, the Ca²⁺ influx induced by cocaine can activate CaMKII. Furthermore, the autophosphorylation of CaMKIIα(T286) by Ca²⁺/CaM could enhance the binding of CaMKIIα to D₃Rs, which further stimulates the phosphorylation of D₃Rs and transiently inhibits the efficacy of those receptors (Liu et al., 2009). Hence, the influx of Ca²⁺ induced by cocaine can stimulate CaMKII, which inhibits the activation of D₃R (Avalos-Fuentes et al., 2015). Furthermore, previous studies have shown that injection of CART into the NAc can decrease the phosphorylation of CaMKIIα on threonine (T) 286 and D₃R (Peng et al., 2014; Fu et al., 2016), which demonstrates that CART can inhibit the activation of CaMKII and further favor the activation of D₃R (Figure 2).

THE PUTATIVE MECHANISM BY WHICH CART ATTENUATES THE BEHAVIORAL EFFECT OF DOPAMINE

The influx of DA in the NAc activates the D₁ DA heteroreceptors and desensitizes the D₃ DA autoreceptors, which activate downstream targets, such as CREB expression and Ca²⁺ signaling, and produce LMA. Previous studies have shown that CART attenuates the behavioral effect of cocaine by inhibiting the behavioral effect of DA. However, the mechanisms through which CART inhibits the behavioral effect of DA are not clear. Some research has shown that injecting CART into the NAc decreases the phosphorylation of CaMKIIα on threonine (T) 286 and D₃R and reduces cocaine-induced LMA (Peng et al., 2014; Fu et al., 2016). Meanwhile, research has demonstrated that injection of the CaMKIIα inhibitor KN-93 into the NAc attenuates cocaine-enhanced locomotion (Kadivar et al., 2014). Together, those results suggest that CART inhibits Ca²⁺ signaling and attenuates the behavioral effect of DA by reducing the phosphorylation

of CaMKII on threonine (T) 286. Specifically, activated CaMKIIα can stimulate the phosphorylation of D₃Rs and transiently inhibit D₃R efficacy (Liu et al., 2009). Meanwhile, D₃Rs could couple with Gi/o proteins and inhibit the cAMP/PKA cascade (Avalos-Fuentes et al., 2015). Considered together, the evidence suggests that CART can inhibit the activation of CaMKIIα and further promote the activation of D₃Rs, which reduce the sensitization response to DA and attenuate the behavioral effect of the neurotransmitter (Figure 2).

FUTURE STUDIES

Since CART was first found to be upregulated by cocaine administration, increasing attention has been paid to the role of CART in cocaine reward (Zhang et al., 2012). Subsequently, other studies have shown that injecting CART into the NAc can attenuate cocaine-induced LMA (Jaworski et al., 2003). By way of explaining this phenomenon further, injecting DA into the NAc results in an increase in LMA, and injecting both DA and CART into the NAc reduces the effect of DA (Kuhar et al., 2005). These findings suggest that CART opposes the actions of cocaine by influencing DA in the NAc. Our previous research has shown that injecting CART into the NAc reduces cocaine-induced LMA by decreasing the phosphorylation of D₃R and the expression of pCaMKIIα (Fu et al., 2016). This result further demonstrates that cocaine-induced LMA also involves CaMKII and D₃R. Furthermore, increasing studies show that GABA_BR may also involve in the mechanistic action of CART in cocaine reward. Previous studies have shown that CART peptides are present in a subset of GABAergic projection neurons that express dynorphin, which inhibits the effect of DA by activating the κ-receptor in the NAc (Dallvechia-Adams et al., 2002; Hubert and Kuhar, 2006). Moreover, CART-containing axons and nerve terminals activate dopaminergic neurons, with some CART peptide-positive terminals forming inhibitory synapses onto GABAergic interneurons in the VTA and substantia nigra (SN; Dallvechia-Adams et al., 2001, 2002). Coincidentally, a previous report (Hubert et al., 2010) has shown that CART-containing terminals that originate in the NAc form symmetric synapses onto inhibitory GABAergic synapses and inhibit cocaine-induced locomotion in the ventral pallidum. These studies suggest that there are functional associations between CART and the GABAergic system (Bäckberg et al., 2003). Meanwhile, some studies have shown that GABA_BR and CART are highly expressed in NAc (Filip and Frankowska, 2008; Hubert et al., 2010; Fu et al., 2016). Furthermore, injecting CART into the NAc increases GABA_BR expression (data not shown). In addition, baclofen (GABA_B receptor agonist) antagonizes cocaine-induced DA release in the NAc and blocks cocaine-induced hyperlocomotion (Filip et al., 2015). Considered together, the evidence suggests that CART may attenuate cocaine-induced locomotion by influencing the expression of GABA_BR. However, further investigations are needed to determine the mechanism by which CART exerts its effect on cocaine-induced locomotion.

Compulsive drug-taking behavior and high rates of relapse are the two main characteristics of drug addiction. Relapse is a difficult problem to solve in drug addiction treatment and occurs when the drug-seeking habit is reactivated by drug-related cues. Initially, the addict may retrieve from memory strongly compelling drug-related experiences, which then lead to further drug-seeking and drug-taking behavior. Currently, research on the effect of CART on cocaine reward mainly focuses on LMA. There are only a few studies on the effect of CART on relapse. James et al. (2010) found that injecting CART into the PVT attenuates cocaine-seeking behavior in rats. However, the mechanism underlying the inhibitory effect of CART on cocaine-seeking behavior remains unclear. Meanwhile, decreased cocaine-seeking behavior induced by CART may involve D₃R and GABA_BR. D₃R agonists and GABA_BR agonists can inhibit cocaine-seeking behavior (Beardsley et al., 2001; Cheung et al., 2013; Blacktop et al., 2016). Furthermore, injecting CART into the NAc decreases the phosphorylation of D₃R (Fu et al., 2016) and increases GABA_BR expression (data not shown).

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AUTHOR CONTRIBUTIONS

CY and XZ wrote the manuscript. ZH provided the idea for this work and designed the structure of the manuscript. The other authors revised the manuscript.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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